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Relevance of vitamin D in muscle health

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Abstract This review will summarize the impact of vitamin D deficiency on muscle health. Mechanistic evidence regarding the presence of the specific vitamin D receptor in muscle tissue and muscle biopsy abnormalities observed with deficiency will be reviewed, as well as molecular and non-molecular effects of vitamin D in muscle tissue. At the clinical level, the evidence from randomized controlled trials of vitamin D supplementation on functional improvement and fall reduction will be summarized. Further, the manuscript will discuss whether vitamin D effects on fall prevention modulate in part its benefit on fracture prevention and why fall prevention is essential in fracture prevention at higher age. Finally, trial and epidemiological data will be reviewed to assess desirable serum 25-hydroxyvitamin D levels for optimal muscle health.

Keywords Vitamin D · Falls · Muscle strength · Bone density · Fractures

1 Introduction

Four lines of evidence support a role of vitamin D in muscle health. *First*, proximal muscle weakness is a prominent feature of the clinical syndrome of vitamin D deficiency [1]. Clinical findings in vitamin D deficiency myopathy include proximal muscle weakness, diffuse muscle pain, and gait impairments such as waddling way of walking [2]. *Second*, the vitamin D receptor (VDR) is expressed in human muscle tissue [3, 4], and VDR activation may promote *de novo* protein synthesis in muscle [5, 6]. Mice lacking the VDR show a skeletal muscle phenotype with smaller and variable muscle fibers and persistence of immature muscle gene expression during adult life [7, 8]. These abnormalities persist after correction of systemic calcium metabolism by a rescue diet [8]. *Third*, several observational studies suggest a positive association between 25-hydroxyvitamin D (25(OH)D) and muscle strength or lower extremity function in older persons [9, 10]. *Fourth*, vitamin D supplementation increases muscle strength and balance [11, 12], and reduces the risk of falling in community-dwelling individuals [12–14], as well as in institutionalized individuals [11, 15] in several double-blind randomized-controlled trials (RCTs) summarized in a 2009 meta-analysis discussed below [16].

1.1 VDR in skeletal muscle tissue

The presence of the VDR in skeletal muscle tissue has been questioned recently by Wang and DeLuca suggesting that the VDR is undetectable in muscle tissue [17]. Wang and DeLuca's findings are in contrast with many earlier studies [3, 18–21], including the most recent one by Ceglia and collagues using a new multi-step immunofluorescent technique to detect the VDR in muscle biopsy tissue from older female subjects [4]. Ceglia and collagues used 3 commercially available anti-bodies to the VDR, including the D-6 Santa Cruz monoclonal antibody used by Wang and DeLuca, and detected the VDR in muscle with each of the three anti-bodies [4].

The presence of a nuclear VDR in muscle tissue suggests that the effect of vitamin D on muscle is most likely direct via

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a genomic transcriptional effect. Mechanistically, it has been suggested that 1,25-dihydroxyvitamin D binds to the nuclear VDR in muscle resulting in *de novo* protein synthesis [5, 6]. At a clinical level, this is supported by findings of two small trials in older adults (see paragraph below), which documented an increase in type II muscle fibers after treatment with 1-alpha-calcidiol [22] or vitamin D2 [23].

In addition to the relatively slow genomic effect of vitamin D on muscle mediated by its nuclear receptor, a non-genomic rapid effect of vitamin D on muscle tissue has been suggested. The non-genomic effect has been found to support calcium transport into the muscle cell relevant to muscle contraction [24, 25]. This effect may be mediated by a VDR located in the cell-membrane of muscle fibers as recently suggested by findings from Ceglia and colleagues. Their data support the presence of a VDR in muscle cell nuclei and suggest a peripheral VDR staining pattern unrelated to the nuclei [4].

One study quantified VDR expression in human skeletal muscle tissue biopsies from 32 orthopedic surgery patients by immunohistological staining of the VDR using a monoclonal rat antibody to the VDR (Clone no. 9A7) [3]. In the multivariate analysis, older age was a significant predictor of decreased VDR expression (number of VDR positive nuclei) after controlling for biopsy location (gluteus medius or the transversospinalis muscle), and 25-hydroxyvitamin D status. An age-related decline in VDR expression is supported by studies in rats where VDR expression declined with advancing age in both intestine [26, 27] and bone [26]. Whether vitamin D supplementation increases VDR expression in muscle is not known to date.

1.2 Vitamin D receptor knockout mouse model

Mice lacking the VDR have key abnormalities that may serve as a model of what severe vitamin D deficiency may cause in humans [28]. Further, the ability to maintain calcium homeostasis in these mice by a recue diet allows insight in actions of the VDR that are critical for normal development independent of its role in calcium homeostasis [29, 30]. Based on these studies an important function of the VDR has been identified in several target tissues, including muscle [28]. Compared to their wild type litter mates, mice lacking the VDR have variable muscle fibers that are 20% smaller in diameter at 3 weeks of age (prior to weaning), and this difference is even more pronounced at 8 weeks of age [8]. Notably, these abnormalities in VDR knock-out mice persist after correction of systemic calcium metabolism by a rescue diet [8] and therefore support a role of the VDR in muscle development and maturation that is based on a direct effect of vitamin D on muscle unrelated to calcium metabolism.

1.3 Vitamin D deficiency and type II muscle atrophy in humans

Muscle biopsy studies in humans suggest a potentially selective effect of vitamin D on type II muscle fibers. *First*, patients with osteomalacic myopathy reveal type II muscle atrophy in muscle histology investigations [31]. *Second*, in two smaller clinical trials treatment with 1-alpha-calcidiol [22] or vitamin D2 [23] increased type II muscle fibers in older adults. Sorenson and colleagues performed one small uncontrolled study with muscle biopsies taken at baseline and after 3 month of treatment with 0.5 micrograms of 1-alpha-calcidiol per day in 11 postmenopausal women with osteoporosis [5]. The authors documented a relative change in fiber composition with an increase in the diameter and number of type II muscle fibers after a 3 month of treatment [5]. In the second randomized controlled study among 48 senior stroke survivors by Sato and colleagues, similar findings were observed after 2-years of treatment with 1000 IU ergocalciferol per day [23].

Type II muscle atrophy in profound vitamin D deficiency, and the observed increase of type II fast-twitch muscle fibers with vitamin D treatment from the two small trials fit well with the findings that high dose vitamin D supplementation (700 to 1000 IU per day) reduced the risk of falling by 34% in a meta-analysis of 8 double-blind randomized controlled trials [32] (see section on fall prevention below). Type II muscle fibers are fast-twitch fibers and therefore are the first to be recruited when fast reaction is needed, such as in the prevention of a fall. Notably, ageing itself has been associated with a decrease in type II fast-twitch relative to type I slow-twitch muscle fibers [33]. Given the high prevalence of vitamin D deficiency in senior adults, it is possible that the age related decline in type II muscle fibers is in part explained by vitamin D deficiency, which may be accompanied by a decrease in muscular VDR expression with age [3].

1.4 Is there 1-alpha hydroxylase activity in muscle?

The 1α-hydroxylase enzyme (CYP27B1) performs the conversion of 25(OH)D into 1,25(OH)2D. Its classic location is the kidney, however more recently the enzyme has been observed in many human cells and tissues [34] including vascular smooth muscle cells [35]. Whether 1α-hydroxylase activity is present also in skeletal muscle is undefined to date.

Children with 1α-hydroxylase deficiency due to mutations in the enzyme (vitamin D dependent rickets type 1/pseudovitamin D deficiency rickets) present with a clinical picture of joint pain and deformity, hypotonia, growth failure and muscle weakness [36]. Notably, muscle weakness in these children is rapidly reversible with physiologic doses of calcitriol or 1α-hydroxyvitamin D [37]. In support of a

concept that the 1α-hydroxylase activity is present in muscle tissue, myopathy in patients with "regular" vitamin D deficiency rickets or osteomalacia is reversible with cholecalciferol or ergocalciferol supplementation [2, 38].

1.5 Vitamin D and function and strength

Most observational studies show a positive association between higher 25(OH)D status and better lower extremity function in older adults. Higher 25(OH)D levels were associated with a lower risk of functional decline [39, 40], a lower risk of future falls and a lower risk of nursing care admission [41], including two population-based studies from the US [10] and Europe [39].

Consistently, in several trials of older individuals at risk for vitamin D deficiency, vitamin D supplementation improved strength, function, and balance [11, 12, 14]. Most importantly, these benefits translated in a reduction in falls in some of the same trials [11, 12, 14]. In three recent double-blind RCTs supplementation with 800 IU vitamin D3 resulted in a 4–11% gain in lower extremity strength or function [11, 12], and an up to 28% improvement in body sway [12, 14] in older adults age 65+ within 2 to 12 month of treatment. Extending to trials among individuals with a lower risk of vitamin D deficiency and including open design trials, a recent meta-analysis by Stockton identified 17 RCTs that tested any form of vitamin D treatment and documented a muscle strength related endpoint. The authors suggested that based on their pooled findings, vitamin D may not improve grip strength, but a benefit of vitamin D treatment on lower extremity strength could not be excluded (p=0.07) among individuals with 25(OH)D starting levels of >25 nmol/l and the authors report a significant benefit among two studies with participants that started with 25(OH)D levels <25 nmol/l [42].

1.6 Vitamin D benefits on fracture prevention may be in part explained by muscle benefit

The beneficial effect of vitamin D on calcium absorption and bone mineral density may not be the only explanation for its protective effect against fractures [43]. In fact, vitamin D deficiency may cause muscular impairment even before adverse effects on bone occur [44]. Further, supported by the presence of the VDR in human muscle tissue [3] and an early (within 2 to 5 months) [11, 15] and sustained [13, 45–47] effect of vitamin D on falls [16], the observed fracture reduction with vitamin D may be modulated in part by its benefit on muscle. Moreover, the early effect of vitamin D supplementation on fall prevention [16] may explain a fracture reduction that was apparent within 6 months of treatment in the Boston STOP-IT [48] and the Decalyos I studies [49].

A dual-benefit vitamin D on bone and muscle is especially attractive among seniors who have a high incidence of non-skeletal risk factors for fracture [50]. Mechanistically, fractures at later age are closely linked to muscle weakness [51] and falling [52, 53]. Over 90% of fractures occur after a fall and fall rates increase with age [54] and poor muscle strength or function [54]. While the circumstances [50] and the direction [55] of a fall determine the type of fracture, bone density and factors that attenuate a fall, such as better strength or better padding, critically determine whether a fracture will take place when the faller lands on a certain bone [56]. Additionally, fear of falling may adversely affect bone density through self-restriction of physical activity [57, 58]. After their first fall, about 30% of persons develop fear of falling [57], resulting in decreased mobility and quality of life [57]. Notably, anti-resorptive therapy alone is not adequate treatment in elders with muscle weakness and other risk factors for falls [59].

1.7 Anti-fall efficacy of vitamin D

Several recent peer-reviewed meta-analyses of randomized, controlled trials have addressed the effect of vitamin D on fall risk reduction [16, 60–67], all of them suggesting a benefit. Thus, given the available evidence today, vitamin D supplementation for fall prevention should not be delayed as a recommendation among the senior population. This suggestion is in line with the Agency for Healthcare Research and Quality (AHRQ) for the U.S. Preventive Services Task Force [66], the 2010 American Geriatric Society/British Geriatric Society Clinical Practice Guideline [68], the 2010 assessment by the IOF [69], and the 2011 recommendations on vitamin D by the Endocrine Society [70], all 4 of which identified vitamin D as an effective intervention to prevent falling in older adults.

Challenging for their assessment is that falls tend to be forgotten if not associated with significant injury [71], requiring short periods of follow-up and well defined ascertainment strategies. Thus, one recent meta-analysis assessed the efficacy of vitamin D supplementation based on double-blind RCTs that also used a high quality fall assessment [16, 32]. Notably, restricting the evidence to double-blind RCTs with a high-quality fall assessment, fall prevention was observed only in trials with a treatment dose of 700 to 1000 IU vitamin D per day [32]. Any lower dose of vitamin D supplementation did not reduce fall risk (see Fig. 1).

The recent 2010 Institute of Medicine (IOM) Report claimed that the peer-reviewed meta-analysis illustrated in Fig. 1 may have been flawed regarding the choice of 8 trials and the method chosen to explain heterogeneity. In a rebuttal [32], the authors confirmed their selection of trials

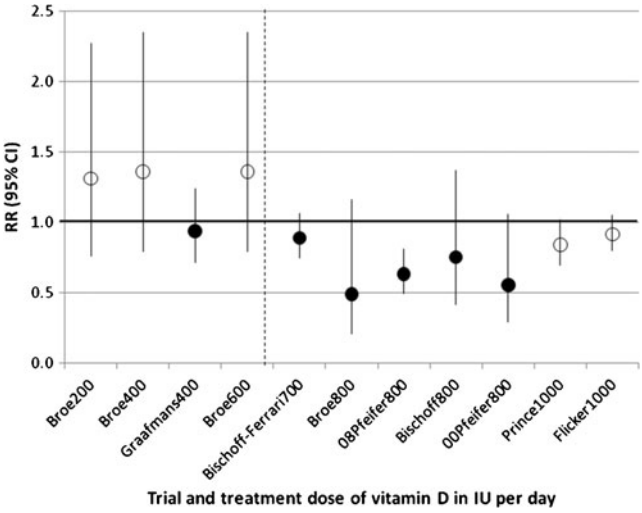

Fig. 1 Fall prevention by dose of vitamin D. Circles show the relative risk of falling in 8 double-blind RCTs testing vitamin D supplementation with or without calcium supplementation against calcium or placebo. Markers filled indicate trials with oral vitamin D3 (cholecalciferol) and markers unfilled indicate trials with oral vitamin D2 (ergocalciferol) [16, 32]. By visual inspection, fall reduction only occurs in trials that tested a vitamin D dose of at least 700 IU per day. Including all trials (regardless of dose level), there was a significant reduction in the odds of falling: OR=0.73 [.62, .87]; p=.0004. When the model is expanded to capture the impact of both high dose and low dose treatment, high dose vitamin D (700 to 1000 IU vitamin D per day) reduced the odds of falling (OR=0.66 [.53, .82] p=.0002), while low dose vitamin D did not (OR=1.14 [.69, 1.87]; p=.61)

and re-analyzed their data to account for the stochastic dependencies (correlations) between the corresponding risk ratios in the multiple dosing trial by Broe et al. as suggested by the IOM. In the re-analysis, when treatment was the only predictor (regardless of dose level), there was a significant reduction in the odds of falling based on the primary analysis of the same 8 trials: OR=0.73 [.62, .87]; p=.0004. When the model was expanded to capture the impact of both high dose and low dose treatment (see Fig. 1), high dose vitamin D (700 to 1000 IU vitamin D per day) reduced the odds of falling by 34% (OR=0.66 [.53, .82] p=.0002), while low dose vitamin D did not (OR=1.14 [.69, 1.87]; p=.61) [32].

Notably, in the original publication of this meta-analysis [16], the authors performed a sensitivity analysis including 15 trials of any study design and fall assessment quality (n= 17,786) and documented a non-significant 7% fall reduction with vitamin D (RR=0.93; 95% CI 0.87–1.01). Even at the comprehensive analysis level, significant variation among the 15 trials (Q-test: p=0.009), could be explained by dose (700 IU +/day; n=17,281; pooled RR was 0.92 (95% CI, 0.85–1.00)), and further among trials that tested a higher dose by trial quality (Q-test: p=0.005). Further, based on the primary analysis [16], the benefit of fall prevention was present in all subgroups of the senior population at the higher dose of vitamin D. At the higher dose of 700 to 1000 IU vitamin D, there was a 38% reduction in the risk of falling with a treatment duration of 2 to 5 months and a sustained significant effect of 17% fall reduction with treatment duration of 12 to 36 months, and the benefit was independent of type of dwelling and age. There was a suggestion that vitamin D_3 was superior to vitamin D_2 for fall prevention. Although the number of studies for active vitamin D and fall prevention was small, the authors pooled these trials separately and found a significant benefit on fall prevention (−22%), which adds to the evidence that improved vitamin D status will reduce the risk of falling in older individuals.

1.8 Summary of the IOM report recommendations of vitamin D and fall prevention

The IOM did a thorough review on the effect of vitamin D on fall prevention. Their synopsis is that the evidence of vitamin D on fall prevention is inconsistent, which is in contrast to all published and peer-reviewed meta-analyses [16, 60–67] and recent guidelines by the Agency for Healthcare Research and Quality (AHRQ) for the U.S. Preventive Services Task Force [66], the American Geriatric Society/British Geriatric Society Clinical Practice Guideline [68], position paper on vitamin D by the IOF [69], and the Endocrine Society [70].

The IOM overall analysis of 12 RCTs (n=14,101) showed a significant benefit of vitamin D on fall prevention (OR=0.89; 95% CI 0.80–0.99), as did the majority of their subset analyses, clearly supporting the use of vitamin D in the prevention of falling. The set of analyses which showed

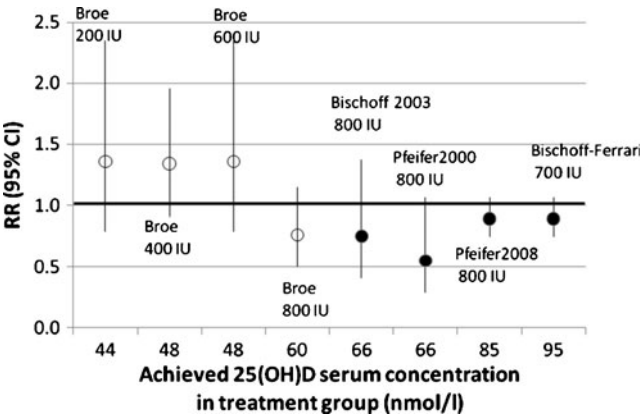

Fig. 2 Fall prevention by achieved 25(OH)D levels. Circles show the relative risk of falling in 5 double-blind RCTs testing vitamin D supplementation with or without calcium supplementation against calcium or placebo documenting achieved 25(OH)D levels in the treatment groups. Markers filled indicate trials with oral vitamin D3 (cholecalciferol) and markers unfilled indicate trials with oral vitamin D2 (ergocalciferol) [16, 32]. By visual inspection, fall reduction only occurs in trials that achieve 25(OH)D levels of at least 60 nmol/l in their treatment groups. Achieved serum 25-hydroxyvitamin D concentrations of 60 nmol/l or more resulted in 23% fall reduction (pooled RR=0.77; 95% CI; 0.65–0.90), while less than 60 nmol/l resulted in no fall reduction (pooled RR=1.35, 95% CI, 0.98–1.84) [10]

no benefit were based on only 4 studies, which cannot be considered reliable indicators of true treatment efficacy, as these trials either used low dose vitamin D [72], had less than 50% adherence [73], had a low-quality fall assessment [74] or used one large bolus dose of vitamin D among seniors in unstable health [75].

1.9 Desirable 25-hydroxyvitamin D status for muscle health

A threshold for serum 25(OH)D level needed for muscle function and fall prevention in older subjects has been evaluated in few studies. A dose–response relationship between lower extremity function and serum 25(OH)D levels has been found in two epidemiologic studies among older individuals [9, 10]. From these analyses a threshold of 50 nmol/l has been suggested for optimal function in one study [9], while in the larger study [10], a threshold beyond which function would not further improve was not identified, but most of the improvement was seen coming from very low 25(OH)D levels to a minimal threshold of 60 nmol/l [10]. Consistently, one meta-analysis of double-blind RCTs found a differential benefit of achieved 25(OH)D levels below 60 nmol/l *versus* levels 60 nmol/l or above, with a benefit demonstrated only in the higher group. Achieved serum 25-hydroxyvitamin D concentrations of 60 nmol/l or more resulted in 23% fall reduction (pooled RR=0.77; 95% CI; 0.65–0.90), while less than 60 nmol/l resulted in no fall reduction (pooled RR=1.35, 95% CI, 0.98–1.84) [10]; see Fig. 2.

Lending further support to the importance of an adequate dose of vitamin D, several double-blind RCTs have documented fracture prevention with 700–800 IU vitamin D per day [48, 49, 74, 76] but not with 400 IU per day [77–79].

2 Conclusion

Vitamin D is relevant to muscle health as supported by several lines of evidence summarized in this article. Based on available data, the VDR is present in muscle tissue and vitamin D effects on muscle are direct including both genomic and non-genomic effects. Strong evidence is available from clinical trials in the senior population suggesting that vitamin D supplementation at a high enough dose reduces the risk of falling. Thus, given the available evidence today, vitamin D supplementation for fall prevention should not be delayed as a recommendation among the senior population. More studies are needed to test whether higher doses of vitamin D than currently recommended (600 to 800 IU/day) contribute to a greater benefit on muscle, including both muscle function and fall prevention. Further, additional studies are needed to further defined vitamin D effects at the cellular level in muscle and whether VDR expression can be enhanced by treatment.

References

1. Al-Shoha A, Qiu S, Palnitkar S, Rao DS. Osteomalacia with bone marrow fibrosis due to severe vitamin D deficiency after a gastrointestinal bypass operation for severe obesity. Endocr Pract. 2009;15:528–33.
2. Schott GD, Wills MR. Muscle weakness in osteomalacia. Lancet. 1976;1:626–9.
3. Bischoff-Ferrari HA, Borchers M, Gudat F, Durmuller U, Stahelin HB, Dick W. Vitamin D receptor expression in human muscle tissue decreases with age. J Bone Miner Res. 2004;19:265–9.
4. Ceglia L, da Silva Morais M, Park LK, Morris E, Harris SS, Bischoff-Ferrari HA, et al. Multi-step immunofluorescent analysis of vitamin D receptor loci and myosin heavy chain isoforms in human skeletal muscle. J Mol Histol. 2010;41:137–42.
5. Sorensen OH, Lund B, Saltin B, Andersen RB, Hjorth L, Melsen F, et al. Myopathy in bone loss of ageing: Improvement by treatment with 1 alpha-hydroxycholecalciferol and calcium. Clin Sci (Colch). 1979;56:157–61.
6. Freedman LP. Transcriptional targets of the vitamin D3 receptor-mediating cell cycle arrest and differentiation. J Nutr. 1999;129:581S–6S.
7. Bouillon R, Bischoff-Ferrari H, Willett W. Vitamin D and health: Perspectives from mice and man. J Bone Miner Res. 2008;28:28.
8. Endo I, Inoue D, Mitsui T, Umaki Y, Akaike M, Yoshizawa T, et al. Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. Endocrinology. 2003;144:5138–44. Epub 2003 Aug 5113.
9. Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J, et al. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab. 2007;6:6.
10. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > =60 y. Am J Clin Nutr. 2004;80:752–8.
11. Bischoff HA, Stahelin HB, Dick W, Akos R, Knecht M, Salis C, et al. Effects of vitamin D and calcium supplementation on falls: A randomized controlled trial. J Bone Miner Res. 2003;18:343–51.
12. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int. 2008;16:16.
13. Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: A 3-year randomized controlled trial. Arch Intern Med. 2006;166:424–30.
14. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res. 2000;15:1113–8.
15. Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of vitamin d reduces the risk of falls in nursing home residents: A randomized, multiple-dose study. J Am Geriatr Soc. 2007;55:234–9.
16. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, et al. Fall prevention with supplemental and active forms of vitamin D: A meta-analysis of randomised controlled trials. BMJ. 2009;339:339. b3692.
17. Wang Y, DeLuca HF. Is the vitamin d receptor found in muscle? Endocrinology. 2011;152:354–63.
18. Bischoff HA, Borchers M, Gudat F, Duermueller U, Theiler R, Stahelin HB, et al. *In situ* detection of 1,25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue. Histochem J. 2001;33:19–24.

19. Boland R. Role of vitamin D in skeletal muscle function. Endocr Rev. 1986;7:434–48.
20. Costa EM, Blau HM, Feldman D. 1,25-dihydroxyvitamin D3 receptors and hormonal responses in cloned human skeletal muscle cells. Endocrinology. 1986;119:2214–20.
21. Simpson RU, Thomas GA, Arnold AJ. Identification of 1,25-dihydroxyvitamin D3 receptors and activities in muscle. J Biol Chem. 1985;260:8882–91.
22. Sorensen OH, Lund B, Saltin B, Andersen RB, Hjorth L, Melsen F, et al. Myopathy in bone loss of ageing: Improvement by treatment with 1 alpha-hydroxycholecalciferol and calcium. Clin Sci (Lond). 1979;56:157–61.
23. Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: A randomized controlled trial. Cerebrovasc Dis. 2005;20:187–92.
24. de Boland AR, Boland RL. Rapid changes in skeletal muscle calcium uptake induced *in vitro* by 1,25-dihydroxyvitamin D3 are suppressed by calcium channel blockers. Endocrinology. 1987;120:1858–64.
25. Vazquez G, de Boland AR, Boland R. Stimulation of Ca2+ release-activated Ca2+ channels as a potential mechanism involved in non-genomic 1,25(OH)2-vitamin D3-induced Ca2+ entry in skeletal muscle cells. Biochem Biophys Res Commun. 1997;239:562–5.
26. Horst RL, Goff JP, Reinhardt TA. Advancing age results in reduction of intestinal and bone 1,25-dihydroxyvitamin D receptor. Endocrinology. 1990;126:1053–7.
27. Gonzalez Pardo V, Boland R, de Boland AR. Vitamin D receptor levels and binding are reduced in aged rat intestinal subcellular fractions. Biogerontology. 2008;9:109–18.
28. Bouillon R, Bischoff-Ferrari H, Willett W. Vitamin D and health: Perspectives from mice and man. J Bone Miner Res. 2008;23:974–9.
29. Li YC, Amling M, Pirro AE, Priemel M, Meuse J, Baron R, et al. Normalization of mineral ion homeostasis by dietary means prevents hyperparathyroidism, rickets, and osteomalacia, but not alopecia in vitamin D receptor-ablated mice. Endocrinology. 1998;139:4391–6.
30. Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and human health: Lessons from vitamin D receptor null mice. Endocr Rev. 2008;29:726–76.
31. Yoshikawa S, Nakamura T, Tanabe H, Imamura T. Osteomalacic myopathy. Endocrinol Jpn. 1979;26:65–72.
32. Bischoff-Ferrari HA, Willett WC, Orav EJ, Kiel DP, Dawson-Hughes B (2011) Re: Fall prevention with Vitamin D. Clarifications needed. http://www.bmj.com/content/339/bmj.b3692/reply
33. Grimby G, Saltin B. The ageing muscle. Clin Physiol. 1983;3:209–18.
34. Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Stewart PM, et al. Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. J Clin Endocrinol Metab. 2001;86:888–94.
35. Somjen D, Weisman Y, Kohen F, Gayer B, Limor R, Sharon O, et al. 25-hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. Circulation. 2005;111:1666–71.
36. Malloy PJ, Feldman D. Genetic disorders and defects in vitamin d action. Endocrinol Metab Clin North Am, 39:333–346, table of contents.
37. Delvin EE, Glorieux FH, Marie PJ, Pettifor JM. Vitamin D dependency: Replacement therapy with calcitriol? J Pediatr. 1981;99:26–34.
38. Al-Said YA, Al-Rached HS, Al-Qahtani HA, Jan MM. Severe proximal myopathy with remarkable recovery after vitamin D treatment. Can J Neurol Sci. 2009;36:336–9.
39. Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J, et al. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab. 2007;92:2058–65.
40. LeBoff MS, Hawkes WG, Glowacki J, Yu-Yahiro J, Hurwitz S, Magaziner J. Vitamin D-deficiency and post-fracture changes in lower extremity function and falls in women with hip fractures. Osteoporos Int. 2008;19:1283–90.
41. Visser M, Deeg DJ, Puts MT, Seidell JC, Lips P. Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission. Am J Clin Nutr. 2006;84:616–22. quiz 671–612.
42. Stockton KA, Mengersen K, Paratz JD, Kandiah D, Bennell KL. Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. Osteoporos Int, 22:859–871.
43. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: A meta-analysis of randomized controlled trials. Arch Intern Med. 2009;169:551–61.
44. Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, Andersen H, et al. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. Calcif Tissue Int. 2000;66:419–24.
45. Flicker L, MacInnis RJ, Stein MS, Scherer SC, Mead KE, Nowson CA, Thomas J, Lowndes C, Hopper JL, Wark JD. Should all older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. JBMR, 2004;19 (Suppl. 1), abstract F459, S99.
46. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: Results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med. 2006;166:869–75.
47. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int. 2009;20:315–22.
48. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997;337:670–6.
49. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med. 1992;327:1637–42.
50. Cummings SR, Nevitt MC. Non-skeletal determinants of fractures: The potential importance of the mechanics of falls. Study of Osteoporotic Fractures Research Group. Osteoporos Int. 1994;4 Suppl 1:67–70.
51. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995;332:767–73.
52. Fatalities and injuries from falls among older adults–United States, 1993–2003 and 2001–2005. MMWR Morb Mortal Wkly Rep. 2006;55:1221–1224.
53. Schwartz AV, Nevitt MC, Brown Jr BW, Kelsey JL. Increased falling as a risk factor for fracture among older women: The study of osteoporotic fractures. Am J Epidemiol. 2005;161:180–5.
54. Tinetti ME. Risk factors for falls among elderly persons living in the community. N Engl J Med. 1988;319:1701–7.
55. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of a nomogram for individualizing hip fracture risk in men and women. Osteoporos Int. 2007;17:17.
56. Nevitt MC, Cummings SR. Type of fall and risk of hip and wrist fractures: The study of osteoporotic fractures. The Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc. 1993;41:1226–34.
57. Vellas BJ, Wayne SJ, Romero LJ, Baumgartner RN, Garry PJ. Fear of falling and restriction of mobility in elderly fallers. Age Ageing. 1997;26:189–93.

58. Arfken CL, Lach HW, Birge SJ, Miller JP. The prevalence and correlates of fear of falling in elderly persons living in the community. Am J Public Health. 1994;84:565–70.
59. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001;344:333–40.
60. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of vitamin D on falls: A meta-analysis. JAMA. 2004;291:1999–2006.
61. Jackson C, Gaugris S, Sen SS, Hosking D. The effect of cholecalciferol (vitamin D3) on the risk of fall and fracture: A meta-analysis. Qjm. 2007;100:185–92.
62. Kalyani RR, Stein B, Valiyil R, Manno R, Maynard JW, Crews DC. Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis. J Am Geriatr Soc, 58, 1299–1310.
63. O'Donnell S, Moher D, Thomas K, Hanley DA, Cranney A. Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls. J Bone Miner Metab. 2008; 26:531–42.
64. Richy F, Dukas L, Schacht E. Differential effects of D-hormone analogs and native vitamin D on the risk of falls: A comparative meta-analysis. Calcif Tissue Int. 2008;82:102–7.
65. Michael YL, Lin JS, Whitlock EP, Gold R, Fu R, O'Connor EA, Zuber SP, Beil TL, Lutz KW. Interventions to prevent falls in older adults: An updated systematic review. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews, 2011
66. Michael YL, Whitlock EP, Lin JS, Fu R, O'Connor EA, Gold R. Primary care-relevant interventions to prevent falling in older adults: A systematic evidence review for the U.S. Preventive services task force. Ann Intern Med. 2011;153:815–25.
67. Cameron ID, Murray GR, Gillespie LD, Robertson MC, Hill KD, Cumming RG, Kerse N. Interventions for preventing falls in older people in nursing care facilities and hospitals. Cochrane Database Syst Rev, CD005465
68. AGS/BGS. (2010) AGS/BGS Guidelines on Fall Prevention in older Persons. http://www.americangeriatrics.org/files/documents/health_care_pros/Falls.Summary.Guide.pdf
69. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, et al. IOF position statement: Vitamin D recommendations for older adults. Osteoporos Int. 2010; 21:1151–4.
70. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin d deficiency: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911–30.
71. Cummings SR, Nevitt MC, Kidd S. Forgetting falls. The limited accuracy of recall of falls in the elderly. J Am Geriatr Soc. 1988;36:613–6.
72. Graafmans WC, Ooms ME, Hofstee HM, Bezemer PD, Bouter LM, Lips P. Falls in the elderly: A prospective study of risk factors and risk profiles. Am J Epidemiol. 1996;143:1129–36.
73. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): A randomised placebo-controlled trial. Lancet. 2005;365:1621–8.
74. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: Randomised double blind controlled trial. BMJ. 2003;326:469.
75. Latham NK, Anderson CS, Lee A, Bennett DA, Moseley A, Cameron ID. A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: The Frailty Interventions Trial in Elderly Subjects (FITNESS). J Am Geriatr Soc. 2003;51:291–9.
76. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: A meta-analysis of randomized controlled trials. Jama. 2005;293:2257–64.
77. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med. 1996;124:400–6.
78. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. J Bone Miner Res. 2002;17:709–15.
79. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354:669–83.